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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/478,621	01/05/2000	Stephen E. Epstein	674522-2001	1917

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EXAMINER
JIANG, DONG

ART UNIT	PAPER NUMBER
1646	20

DATE MAILED: 08/27/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/478,621	Applicant(s) EPSTEIN ET AL.	
	Examiner Dong Jiang	Art Unit 1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 June 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-5 and 8-33* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 3-5, 8-11 and 18-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1,3-5 and 8-33* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED OFFICE ACTION

The request filed on 25 June 2003 (paper No. 18) for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/478,621 is acceptable and a CPA has been established. An action on the CPA follows.

Applicant's amendment and response in paper No. 19, filed on 25 June 2003 is acknowledged and entered. Following the amendment, the new claims 18-33 are added.

Currently claims 1, 3-5 and 8-33 are pending, and claims 1, 3-5, 8-11 and 18-33 are under consideration.

Objections and Rejections under 35 U.S.C. 112:

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 3-5, 8-11, and 18-33 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 and 18 recite the limitation of "reducing or treating restenosis". The term "restenosis" may be used to indicate many different types of pathological conditions besides coronary restenosis, such as restenosis of a heart valve. The specification merely suggests coronary restenosis. As such, the claims fail to adequately point out that which applicants see as their invention.

The remaining claims are rejected for depending from an indefinite claim.

Rejections Over Prior Art:

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 3-5, and 8-11 are rejected, and claims 18-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Inoue et al. (Circulation, Nov. 1998, 98(20): 2108-16), and Maisonpierre et al. (Science, July 1997, 277:55-60), in view of Kendall et al. (US 5,712,380), and Asahara et al. (Circ. Res., 1998, 83: 233-240), for the reasons set forth in the previous Office Actions, paper No. 9, at pages 6-8, and paper No. 13, at pages 4-6, and further in view of Hanahan (Science, 1997, 277: 48-50).

The teachings of Inoue, Maisonpierre, Kendall, and Asahara are reviewed in the previous Office Action, paper No. 9.

Hanahan teaches that Ang1 signals Tie2 (receptor) to recruit support cells (page 49, the left column, lines 17-18), and appears to mediated vessel maturation ..., and the maintenance of those vessels (page 49, the middle column, lines 7-12 of the second paragraph, and Figure 2), and that Ang2 blocks the Ang1/Tie2 signal, resulting in a loosing of the tight vascular structure and thereby exposing the endothelial cells to activating signals from angiogenesis inducers, including VEGF, and if VEGF is present, the endothelial cells become activated to migrate and proliferate, producing new capillary sprouts and in turn tubes (page 49, the right column, lines 3-12).

Applicants argument, filed on 25 June 2003 (paper No. 19), has been fully considered, but is not deemed persuasive for reasons below.

With respect to the Inoue reference, applicants argue, at page 4 of the response, that the reference merely demonstrates the expression of VEGF, suggesting that VEGF may have some

role in atherosclerosis, and it does not establish any cause/effect relationship, as Inoue discusses two possibilities: that increasing angiogenesis causes plaque growth; and that the growing atherosclerotic plaque delivers signal causing plaque the development of blood vessels. This argument is not persuasive because the cause/effect relationship is not so relevant as the fact is, with either of the two possibilities, angiogenesis or the development of blood vessels is a part of the pathology of atherosclerosis. As it is well established in the art that VEGF promotes angiogenesis, it would be instantly obvious to a person of ordinary skill in the art that inhibition of VEGF would be beneficial in treating atherosclerosis. Applicants further argue, at page 5 of the response, that VEGF is a potent chemoattractant of monocytes/macrophages, which present in the vessel wall critically contribute to the development of atherosclerosis, that the presence of VEGF in an atherosclerotic plaque might therefore be causally related to growth of the plaque, but not because of its effect on angiognesis, and that Inoue does not even definitely demonstrates that VEGF contributes to atherosclerosis by the increase development of plaque blood vessels. This argument is not persuasive because, once again, it is less relevant as to through what mechanism(s) VEGF contributes to the development of the plaque, as long as it is in agreement that VEGF has a role in the development of the plaque, whether it does it through recruiting macrophages or increasing development of plaque blood vessels. Therefore, incorporating the inhibition of VEGF in the treatment strategy becomes obvious, especially that VEGF seems to be involved in multiple events contributing to the development of the plaque.

With respect to the Kendall reference, applicants argue, at page 5 of the response, that the reference only shows that a VEGF inhibitor can inhibit mitogenesis, and that nowhere in the reference does Kendall teach or suggest the use of a VEGF inhibitor to treat restenosis or atherosclerosis, nor the combination of a VEGF inhibitor with another molecule. This argument is not persuasive because *the point to learn* from the Kendall reference is not whether that a VEGF inhibitor should be used to treat restenosis or atherosclerosis, rather, it is that *a soluble VEGF receptor can serve as a VEGF inhibitor* (column 8, lines 57-58), and a VEGF inhibitor would be useful as a treatment for persistent pathological angiogenesis (column 1, lines 39-45). *Together with other cited references*, they make the present claims obvious. Further, if Kendall had taught the combination of a VEGF inhibitor with another molecule such as a angiopoietin, the claims would have been rejected under 35 U.S.C. 102 for being anticipated by the reference.

With respect to the Maisonpierre reference, applicants argue, at page 5 of the response, that while the reference suggest opposing roles for Ang1 and Ang2, and that simultaneous regulation of VEGF and angiopoientins may positively promote revascularization or negatively prevent tumor growth, it does not suggest that the combination can reduce or treat restenosis or atherosclerosis or plaque formation. This argument is not persuasive because *the points to learn* from the Maisonpierre reference are that Ang1 and Ang2 have opposing roles, and that therapeutic manipulation of vessel growth, - either positively or negatively, - is likely to require *simultaneous regulation of both* the VEGF and angiopoietin systems. Maisonpierre's teachings made a combination therapy manipulating both VEGF and angiopoietin instantly obvious.

With respect to the Asahara reference, applicants argue, in the paragraph bridging pages 5 and 6 of the response, that the reference provides no data, teaching or suggestions on the combination of a VEGF inhibitor and angiopoietin, and that Asahara 's findings relate neither to restenosis nor to atherosclerosis, and there is no evidence that the growing plaque blood vessels causes the plaque growth. This argument is not persuasive because while Asahara does not teach the combination of a VEGF inhibitor and angiopoietin (would have been anticipating otherwise), the concept of the combination is conveyed as Asahara teaches that neither ang1 nor ang2 alone promoted neovascularization (line 7 of the abstract), and that ang2 + VEGF promoted significantly longer and more circumferential neovascularity. Therefore, one must inhibit both VEGF and Ang2 in order to effectively reduce neovascularization. Further, although Asahara does not teach angiogenesis in restenosis or atherosclerosis exclusively, other cited reference, such as the Inoue reference, teaches that VEGF is capable of inducing neointimal angiogenesis and intimal hyperplasia, and may promote process of atherosclerosis, and that the coronary occlusive lesions have extensive neovascularization. Thus, as angiogenesis is a part of the pathology of restenosis or atherosclerosis, a regiment of anti-angiogenesis is indicated and would be beneficial.

As addressed repeatedly in the previous office actions, and the Examiner would like to emphasize once again, that it is the combination of all, not any one of the cited references alone makes the present invention obvious, and each one does not teach all elements in the present claims. Applicants arguments are against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on

combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

At page 6 of the response, applicants argue that it is not obvious to combine Angl and a VEGF inhibitor for reducing or treating restenosis or atherosclerosis, as alone, Angl or Ang2 has no effect on neovascularization, and in combination with VEGF, both Angl and Ang2 increase vascularization, albeit in different ways, i.e., VEGF and Angl increase vascular density, and VEGF and Ang2 increase the extent and length of vasculatur. This argument is not persuasive because in the absence of VEGF (in the situation a VEGF inhibitor is used, for example), Angl would not increase vascularization. As taught by Hanahan, Angl appears to mediated vessel maturation and maintain vessel integrity and quiescence without VEGF (see Figure 2). Therefore, it is logical to block VEGF, and meanwhile to provide Angl to preserve endothelial cell quiescence, which prevent further angiogenesis.

At page 6 of the response, applicants further argue that the cited references neither teach nor suggest reduction or treatment of restenosis or atherosclerosis using a VEGF inhibitor and an inducer of vessel maturation, and they also do not even contain concurring results, and that they fail to provide the necessary suggestion of the desirability of the modification of the teachings, and "obvious to try" is not the standard of 103. This argument is not persuasive because if the references had taught reduction or treatment of restenosis or atherosclerosis using a VEGF inhibitor and an inducer of vessel maturation, they would have been anticipating. Further, as the references teach underlying mechanisms of VEGF and/or the angiopoietin systems from different respects, and demonstrate the role of VEGF and/or the angiopoietin systems in angiogenesis or neovascularization, which is indicated in the pathology of restenosis or atherosclerosis, the motivation and a reasonable expectation of success of using a VEGF inhibitor and an inducer of vessel maturation in the treatment of restenosis or atherosclerosis are clearly conveyed by the combination of the references.

At page 6 of the response, applicants further argue that the combined teachings of the references would lead one of skill in the art to the conclusion that the teachings are too diversified and contradictory to provide any expectation of success in providing a treatment for inhibiting tumor growth or corneal vascularization, let alone treatment for conditions which may or may not be related, including restenosis or atherosclerosis. This argument is not persuasive

because what to learn from each reference is not how to treat a condition such as tumor growth alone, the focus is on the impact of VEGF and Ang1/Ang2 systems on regulation of vasculogenesis and angiogenesis, which is common aspect in conditions such as tumor growth and restenosis or atherosclerosis. Therefore, although the cited references do not explicitly mention restenosis or atherosclerosis, the involvement of VEGF and Ang1/Ang2 systems is clearly indicated.

At page 7 of the response, applicants argue that atherosclerosis or restenosis is not the focus of the Maisonpierre or Asahara reference, and therefore, there would be no motivation to combine teachings of the references to arrive at a treatment for restenosis. This argument is not persuasive because restenosis is not a pathology term, and it merely indicates recurrent stenosis (a physical obstruction). Atherosclerosis and coronary restenosis involve common pathology, such as angiogenesis or neovascularization, as indicated by Pels et al. (Japanese Circulation Journal, 1997, 61 (11): 893-904). Pels teaches that neointimal formation and arterial wall remodeling are pivotal causes of luminal narrowing in *atherogenesis and restenosis* (abstract). As such, it is obvious to a person of ordinary skill in the art to extend a treatment for atherosclerosis to treating restenosis.

As summarized in the previous Office Action, suggestion or motivation to use a VEGF inhibitor and Ang1 for reducing and treating restenosis or atherosclerosis can be found based on combined teachings of the cited references, which teach that VEGF is involved in the process of atherosclerosis and neointimal angiogenesis, that the coronary occlusive lesions have extensive neovascularization (by Inoue); that ang-1 and Tie2 receptor play critical roles in angiogenic outgrowth, vessel remodeling, and maturation, that ang-2 is a natural antagonist for ang-1 and the Tie2 receptor, that therapeutic manipulation of vessel growth, is likely to require simultaneous regulation of *both* the VEGF and angiopoietin systems (by Maisonpierre); that Ang1 alone contributes to vessel maturation and endothelial cell quiescence (by Hanahan); that a soluble VEGF receptor would be useful as a treatment for persistent pathological angiogenesis (by Kendall); and that ang2 + VEGF promoted significantly longer and more circumferential neovascularity (by Asahara). It is logical and obvious to a skilled artisan to design a medical intervention to inhibit both ang2 and VEGF for treating atherosclerosis and/or restenosis, and to expect therapeutic effect in individuals with such conditions because the combined teachings from

these references clearly indicate the involvement of VEGF and angiopoietins in atherosclerosis and restenosis.

Conclusion:

No claim is allowed.

Advisory Information:

Any inquiry concerning this communication should be directed to Dong Jiang whose telephone number is 703-305-1345. The examiner can normally be reached on Monday - Friday from 9:00 AM to 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, can be reached on (703) 308-6564. The fax phone number for the organization where this application or proceeding is assigned is 703-308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Lorraine Spector

LORRAINE SPECTOR
PRIMARY EXAMINER

Dong Jiang, Ph.D.
Patent Examiner
AU1646